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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte ANDRE R. ABAD, NICHOLAS B. DUCK, XIANG FENG, RONALD D. FLANNAGAN, THEODORE W. KAHN, and LYNNE E. SIMS

Appeal 2007-4213
Application 10/032,717
Technology Center 1600

Decided: April 3, 2008

Before DONALD E. ADAMS, ERIC GRIMES, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a nucleic acid that encodes a pesticidal polypeptide, which the Examiner has rejected as failing to enable the full scope of the claims and as failing to meet the written description requirement. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

Background

"Insect pests are a major factor in the loss of the world's agricultural crops" (Spec. 1). The Specification discloses that "[c]ertain species of microorganisms of the genus *Bacillus* are known to possess pesticidal activity against a broad range of insect pests" (Spec. 2). The Specification also notes that "agricultural scientists have developed crop plants with enhanced insect resistance by genetically engineering crop plants to produce pesticidal proteins from *Bacillus*" (Spec. 2). According to the Specification, "[s]ome insects, such as Western corn rootworm, have proven to be recalcitrant, and the level of *Bt*-toxin resistance is increasing in formerly susceptible populations of some important insect pests" (Spec. 3).

Appellants teach "nucleic acids, and fragments and variants thereof, which encode polypeptides that possess pesticidal activity against pests of the order Coleoptera. The wild-type (e.g., naturally occurring) nucleotide sequences of the invention, which were obtained from strains of *Bacillus thuringiensis*, encode *Cry*-8-1ike δ-endotoxins" (Spec. 3).

Statement of the Case

The Claims

Claims 1-3, 9-12, 17-19, 38, 43, 46, 49, 52 and 55-64 are on appeal. We will focus on claim 1 which is representative and reads as follows:

> 1. An isolated nucleic acid comprising a nucleotide sequence having at least 90% sequence identity to the nucleotide sequence set forth in SEQ ID NO: 1, wherein said nucleotide sequence encodes a polypeptide which is pesticidal for at least one pest belonging to the order Coleoptera.

The Examiner relies on the following prior art references to show unpatentability:

Sequence Comparison between SEQ ID Nos: 2 and 4

Tounsi et al., *Cloning and study of the expression of a novel cry1Ia-type gene from Bacillus thuringiensis subsp. kurstaki*, 95 J. Applied Microbiology 23-28 (2003).

Minshull et al., *Protein evolution by molecular breeding,* 3 Current Opinion Chem. Biol. 284-290 (1999).

Lazar et al., *Transforming growth factor α: mutation of aspartic acid 47 and Leucine 48 results in different biological activities,* 8 Molecular Cellular Biol. 1247-1252 (1988).

Hill et al., *Functional analysis of conserved histidines in ADP-glucose pyrophosphorylase from Escherichia coli,* 244 Biochemical Biophysical Research Communications 573-577 (1998).

De Maagd et al., *Identification of Bacillus thuringiensis delta endotoxin cry1C domain III amino acid residues involved in insect specificity,* 65 Applied Environ. Microbiology 4369-4374 (1999).

Angsuthanasombat et al., *Directed mutagenesis of the Bacillus thuringiensis cry11A toxin reveals a crucial role in larvicidal activity of arginine-136 in helix 4,* 34 J. Biochemistry Molecular Biol. 402-407 (2001).

Li et al., *Crystal structure of insecticidal δ-endotoxin from Bacillus thuringiensis at 2.5 A resolution,* 353 Nature 815-821 (1991).

The rejections as presented by the Examiner are as follows:

A. Claims 1-3, 9-12, 17-19, 38, 43, 46, 49, 52, and 55-64 stand rejected under 35 U.S.C. § 112, first paragraph as being nonenabled for the full scope of the claims.

B. Claims 1-3, 9-12, 17-19, 38, 43, 46, 49, 52, and 55-64 stand rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement.

A. 35 U.S.C. § 112, first paragraph Enablement rejection

Claims 1-3, 9-12, 17-19, 38, 43, 46, 49, 52, and 55-64 stand rejected under 35 U.S.C. § 112, first paragraph, on the basis that the Specification

> while being enabling for nucleic acids encoding SEQ ID NO:2 and 10, expression cassettes comprising the nucleic acids, plants and seeds comprising a construct comprising the nucleic acid, and a method of using it to impact a plant pest, does not reasonably provide enablement for any nucleic acid that has 90% identity to SEQ ID NO:1, expression cassettes comprising the nucleic acid, plants and seeds comprising a construct comprising the nucleic acid and a method of using it to impact a plant pest.

(Ans. 4.)

The Examiner reasons that the Specification "fails to provide guidance for the full scope of which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional enzyme" (Ans. 5). The Examiner cites Lazar and Hill to demonstrate that even conservative mutations may yield unpredictable results (*see* Ans. 6). The Examiner also contends that

> All the studies on Cry protein structure and *Cry* protein amino acid substitutions look only at the N-terminal half of

> the proteins (See Li et al, Tounsi et al, de Maagd et al, and Angsuthanasombat et al). There is no guidance in the art or the specification for making amino acid substitutions in the C-terminal half; because no guidance is provided, one would have to use trail and error experimentation to make nucleic acid[substitutions] within the full scope of the claims. Multiple amino acid substitutions within the C-terminal half of the *Cry* protein would alter overall protein structure, affecting its stability of the protein and/or availability of the protease site to insect enzymes, thus rendering the protein non-toxic.

(Ans. 15.)

After analyzing the *Wands* factors, the Examiner concludes that to "make nucleic acids with 90%, 93%, 94% or 95% identity to SEQ ID NO: 1 and encoding Coleopteran pesticidal proteins with up to 362, 253, 217 or 181 amino acid substitutions relative to SEQ ID NO:2 would require undue experimentation" (Ans. 28).

Appellants argue that the "specification teaches those skilled in the art how to make the claimed nucleotide sequences and provides examples of such sequences. The specification provides: nucleotide sequences that fall within the scope of the claims . . . [and] guidance regarding alterations that allow the amino acid sequence to retain pesticidal activity" (App. Br. 6). Appellants note that the "it was customary in the art at the time of the invention to make and assay a number of sequences for a desired function in order to achieve the best results" (App. Br. 10).

According to Appellants, the "de Maagd, Tounsi, and Angsuthanasombat references all make substitutions in *Cry* proteins and then test for activity. This is all that is required to test sequences that fall

within the scope of the claims" (App. Br. 11). Appellants argue that "δ-endotoxins are extremely well-characterized and related to various degrees by similarities in their amino acid sequences and tertiary structures." (App. Br. 14). Appellants contend that the Specification demonstrates a number of examples of proteins which differ in sequence from SEQ ID NO: 1, but retain pesticidal function (*see* App. Br. 15).

In view of these conflicting positions, we frame the enablement issue before us as follows:

Would it have required undue experimentation to make and/or use the full scope of a nucleic acid that has at least 90% sequence identity to SEQ ID NO: 1?

Findings of Fact

Breadth of the Claims

1. Claim 1 is not limited to SEQ ID NO: 1, but encompasses any nucleic acids which have a minimum of 90% sequence identity with SEQ ID NO: 1 (*see* Claim 1). Claims 38, 43, 49, 55, 56, 63, and 64 encompass smaller, subgeneric sets of nucleic acids with 93%, 94% or 95% sequence identity with SEQ ID NO: 1.

2. Claim 1 imposes a functional or biological test that requires the sequence to encode a pesticidal protein (*see* Claim 1).

Presence of Working Examples

3. The Specification discloses a number of nucleic acid sequences which fall within the scope of the claims, as working examples, including "the *Cry8*-like nucleotide sequences set forth in SEQ ID NOS: 1, 3, 5, 7, 9, 11, 15, 17, 19, 21, 23, 27, 28, 29, 31, 33, 39, 41, 43, and 45" (Spec. 11).

4. The Specification discloses deletion mutations in the endotoxin of SEQ ID NO: 1 which truncate the endotoxin, where "SEQ ID NOS: 6, 10 and 16 represent a polypeptide that is shortened (truncated) at the 3' end of the amino acid sequence set forth in SEQ ID NO:2. . . . SEQ ID NO: 20 provides a variant that is truncated at both the 5' and 3' ends of the full-length protein set forth in SEQ ID NO:2" (Spec 14:28-15:1).

5. The Specification teaches mutations in the endotoxin of SEQ ID NO: 1 in which protease sites are varied, noting

> SEQ ID NO:12 provides a mutant, referred to herein as NGSR.N1218-1, that comprises an additional trypsin-sensitive cleavage site; SEQ ID NO:22 provides a second mutant, referred to herein as LKMS.N1218-1, that comprises a chymotrypsin-sensitive cleavage site that is not present in the wild-type 1218-1 or 1218-1A polypeptide; and SEQ ID NO:24 provides a replacement mutant, referred to herein as LKMS.R1218-1, in which an existing trypsin cleavage-site is destroyed and a chymotrypsin site is introduced in its place. SEQ ID NO:40 provides a second chymotrypsin-addition mutant, referred to herein as LRMS.N1218-1, that comprises the alternative chymotrypsin cleavage site LRMS (SEQ ID NO:48). SEQ ID NO:44 provides a second replacement or substitution mutant, referred to herein as LRMS.R1218-1, in which the native trypsin site is replaced with the chymotrypsin cleavage site LRMS.

(Spec. 15:9-20).

6. The Specification teaches that a variety of these mutations of SEQ ID NO: 1 retain functional pesticidal activity (Spec. 73, table 1).

Amount of Direction or Guidance Presented

7. The Specification provides general guidance on methods of making mutations (Spec. 23:22-29, 24:15-27).

8. The Specification provides guidance regarding the structure of the endotoxin, noting that a "comparison of the amino acid sequences of *Cry* toxins of different specificities reveals five highly conserved sequence blocks. Structurally, the δ-endotoxins comprise three distinct domains, which are, from the N- to C-termini: a cluster of seven alpha-helices implicated in pore formation, three anti-parallel beta sheets implicated in cell binding, and a beta sandwich." (Spec. 24: 10-14).

9. The Specification teaches that the crystal structure of the *Cry*3A gene was used "to produce a homology model of the *Cry*8 δ-endotoxin disclosed and claimed herein as SEQ ID NO:2 to gain insight into the relationship between structure and function of the endotoxin, and to design the recombinantly engineered proteins" (Spec. 25:2-5).

10. The Specification defines functions of the various domains, teaching "δ -endotoxins isolated from *B. thuringiensis* are generally described as comprising three domains, a seven-helix bundle that is involved in pore formation, a three-sheet domain that has been implicated in receptor binding, and a beta-sandwich motif" (Spec 25:9-12).

11. The Specification exemplifies bioassays which test for the pesticidal activity of mutant polypeptides and which transform plant cells to express the mutant pesticidal polypeptides (Spec 69-77, Examples 7-9).

State of the Prior Art and Unpredictability of the Art

12. De Maagd teaches that

> Progress has been made both in determining the three-dimensional structure of the toxin molecule and in identifying the primary sequences involved in specificity and receptor binding, allowing the study of structure-function relationships. The published structures of two delta-endotoxins show a three-domain structure (8, 10). The N-terminal domain I consists of seven alpha-helices and is thought to be responsible for insertions into the insect cell membrane and to be involved in pore formation. The more variable domain II contains the primary sequences that have been shown to be involved in insect specificity and in high-affinity binding (13). Domain II is therefore assumed to be involved in actual interactions with receptors and, to a large extent, in determining specificity through that process. The function of the C-terminal domain III at the molecular level was unknown until recently, although a variety of mutagenesis and recombination experiments have shown that it can be involved in specificity

(De Maagd 4369, col. 1-2).

13. De Maagd teaches that "we have identified *Cry*1C domain III amino acids in larger blocks (blocks D and E) as well as in small blocks or groups (block C and the insertion in block D) and a single amino acid (Trp-476), which have a strong positive effect on activity against *S. exigua*" (De Maagd 4373, col. 2).

14. De Maagd teaches that some mutations result in loss of pesticidal activity against some organisms "[b]oth deletions (NS13 and NS16) resulted in the loss of activity against *S. exigua*. Alanine substitution of the second group (NS15) also lead to loss of activity, but substitution of the first group (NS14) only slightly affected activity against *S. exigua"* (De Maagd 4372, col. 2).

15. Angsuthanasombat teaches "the three-dimensional structures of two different *Cry* δ-endotoxins, *Cry*1Aa, and *Cry*3A have been solved by X-ray crystallography" (Angsuthanasombat 402-403).

16. Angsuthanasombat teaches that "[b]oth structures display a high degree of overall structural similarity and are composed of three structurally distinct domains. It is apparent that the N-terminal domain, a seven-helix bundle (six amphipathic helices around a central core helix), is clearly equipped for membrane insertion and pore formation" (Angsuthanasombat 403, col. 1).

17. Angsuthanasombat teaches "[b]ased on a multiple-amino acid sequence alignment with the known crystal structures of *Cry*1Aa and *Cry*3A [Refs omitted], and the homology-based model of *Cry*4B [], the predicted α4 and α5 were located within the pore-forming domain of *Cry*11A (see Fig. 1A). Charged amino acids in helix 4 were shown to be critical for toxin activity" (Angsuthanasombat 404, col. 2). Angsuthanasombat further discloses 8 mutations for analysis of toxicity (*see* Angsuthanasombat 404-405).

18. Li teaches the crystal structure of a δ-endotoxin and teaches that the "core of the molecule encompassing all the domain interfaces is built from conserved sequence segments of the active δ–endotoxins. Therefore, the structure represents the general fold of this family of insecticidal proteins" (Li 815, abstract).

19. Tounsi teaches that "[a]lthough delta-endotoxins encoded by *cry1IaI* and *cry1Ia2* genes included single amino acid differences in domain

1, they exhibited a different insecticidal activity spectrum" (Tounsi 27, col. 2).

20. Lazar discloses that even a conservative substitution may result in a change in activity of a protein (*see* Lazar 1247, abstract).

21. Hill teaches regarding mutations in an ADP-glucose pyrophosphorylase enzyme that "asparagine is also a conservative change, but that arginine and aspartate are deleterious to enzyme function" (Hill 576, col. 1).

Quantity of Experimentation necessary

22. Minshull teaches methods of making recombinant molecules which have functions different than the starting materials (Minshull 284).

23. The Specification teaches that "[a]lthough numerous investigators have attempted to make mutant endotoxin proteins with improved insecticidal activity, few have succeeded. In fact, the majority of genetically engineered *B. thuringiensis* toxins that have been reported in the literature report endotoxin activity that is no better than that of the wild-type protein, and in many cases, the activity is decreased or destroyed altogether" (Spec. 3:4-8).

24. The Specification teaches that

> advances in the field of molecular biology such as site-specific and random mutagenesis, polymerase chain reaction methodologies, and protein engineering techniques provide an extensive collection of tools and protocols suitable for use to alter or engineer both the amino acid sequence and underlying genetic sequences, of proteins of agricultural interest. Thus, the *Cry*8-1ike proteins of the invention may be altered in various ways including amino acid

> substitutions, deletions, truncations, and insertions. Methods for such manipulations are generally known in the art.

(Spec. 23:14-21).

25. "For purposes of the present invention, comparison of nucleotide or protein sequences for determination of percent sequence identity to the *Cry8*-like sequences disclosed herein is preferably made using the GAP program in the Wisconsin Genetics Software Package (Version 8 or later) or any equivalent program" (Spec. 36:6-9).

Discussion of 35 U.S.C. § 112, first paragraph Enablement rejection

"The essential question here is whether the scope of enablement … is as broad as the scope of the claim[s]." *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1212 (Fed. Cir. 1991). We agree with the Appellants that it would not have required undue experimentation to practice of the full scope of the claimed invention. We note that if claims with 90% sequence identity are enabled, *a fortiori*, the dependent claims with narrower 93%-95% sequence identity are also enabled.

Other than the fact that molecular biology is an unpredictable art, the remaining *Wands* factors favor Appellants, particularly "the amount of direction or guidance presented", "the state of the prior art" and "the relative skill of those in the art," *In re Wands*, 858 F.2d 731, 736 (Fed. Cir. 1988). Even the factor of "the predictability or unpredictability of the art" weighs in favor of Appellants, as evidenced by the prior art teachings and Appellants' Specification.

> It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Angstadt*, 537 F.2d 498, 502-03,

> 190 USPQ 214, 218 (CCPA 1976). However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill in the art how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility.

In re Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991). In the instant fact pattern, there is significant disclosure of methods for making and screening *Cry* δ-endotoxins that are 90% or more identical to SEQ ID NO: 1 (*see* FF 7, 8, 11, 22, 24, 25).

The claims are drawn to any nucleic acid with at least 90% Sequence identity to SEQ ID NO: 1 that encodes a pesticidal polypeptide (see FF 1-2, Claim 1). The Specification exemplifies a number of mutations, including deletion of regions of the *Cry* δ-endotoxin as well as specific mutations within various domains of the *Cry* δ-endotoxin (FF 3-6). The Specification also provides both specific and generic guidance on methods of making mutations in the *Cry* δ-endotoxin (FF 7). Perhaps more importantly, the Specification provides significant guidance on the structure/function relationships of *Cry* δ-endotoxins (FF 8-10). The Specification expressly discusses particular domains of the protein which are involved in different functional aspects of insecticidal activity, including targeting different insects and maximizing lethality (FF 8-10). Lastly, the Specification provides specific guidance on methods of testing whether specific mutated forms of the *Cry* δ-endotoxin retain pesticidal function (FF 11).

While the Examiner correctly notes that the prior art recognizes that any particular mutation in a protein sequence, even a conservative mutation, may result in an unpredictable change in the activity or function of a particular protein (FF 14, 20, 21), the majority of the prior art that is specific to *Cry* δ-endotoxin discusses the significant structure/function relationships determined for this particular class of proteins (*see* FF 12, 13, 15-19). Besides disclosure of multiple *Cry* δ-endotoxin nucleic acid sequences, Angsuthanasombat also teaches that "the three-dimensional structures of two different *Cry* δ-endotoxins, *Cry*1Aa, and *Cry*3A have been solved by X-ray crystallography" (Angsuthanasombat 402-403). In addition, De Maagd discusses the three different domains within the *Cry* δ-endotoxin as well as specific structural blocks within the third domain (FF 12-14). There is significant discussion in Angsuthanasombat, Li and De Maagd that the structure of domain I of the *Cry* δ-endotoxin is associated with pore formation and that this structure is associated with the function of pesticidal activity (FF 12-18). The prior art and Specification also teach that domain II is a three-sheet domain that has been implicated in receptor binding, and domain III is a beta-sandwich motif that is involved in insect specificity (FF 10, 12-18).

The Specification also teaches that the quantity of experimentation necessary to make and screen mutations in the *Cry* δ-endotoxin is routine in the art (FF 22-24). In addition, the Specification provides express guidance on means to determine if a nucleic acid falls within the scope of the 90% sequence identity language of claim 1 (FF 25).

We are not persuaded by the Examiner's argument that the number of mutations exemplified by Appellants is insufficient because they are focused on the N-terminus of the protein and relate to truncations to the N-terminus of the endotoxin (*see* Ans. 13-15). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984).

We are also not persuaded by the Examiner's argument that making and using the nucleic acids of claim 1 would require undue experimentation because it would require trial and "error experimentation because of the likelihood of protein inactivation and because of the unpredictability of amino acid interactions in *Cry* proteins" (Ans. 17). We think that the evidence shows that synthesis and testing of any particular mutation, or of a job lot of mutations prepared using standard techniques, was routine in the art as of Appellants' filing date (*see* FF 11, 22-25). Further, Appellants and the prior art provide specific guidance on structure/function relationships in the *Cry* δ-endotoxins, to the point where Angsuthanasombat teaches that "[c]harged amino acids in helix 4 were shown to be critical for toxin activity" (Angsuthanasombat 404, col. 2). With specific information on particular helices of the protein which are involved in toxin activity, as well as information regarding domains (FF 12-18), it would have required some experimentation in order to determine which nucleic acids would have pesticide activity and against which pests, but that experimentation would have been routine, not undue. Dr. Abad states regarding production of plants expressing proteins with pesticidal activity that "while it is a time-

consuming and laborious task, it is also considered 'routine' by scientists who are responsible for producing such plants" (Abad Declaration, ¶ 1).

We conclude that the Specification and prior art would have enabled the full scope of claim 1.

We reverse the rejection of claim 1 under 35 U.S.C. § 112, first paragraph, enablement. The rejection of claims 2-3, 9-12, 17-19, 38, 43, 46, 49, 52, and 55-64 is also reversed.

B. 35 U.S.C. § 112, first paragraph written description rejection

Claims 1-3, 9-12, 17-19, 38, 43, 46, 49, 52, and 55-64 stand rejected under 35 U.S.C. § 112, first paragraph, on the basis that

> One of skill in the art would not recognize that Applicant was in possession of the necessary common attributes or features of the genus in view of the disclosed species. Since the disclosure fails to describe the common attributes that identify members of the genus, and because the genus is highly variant, SEQ ID NO: 1 alone is insufficient to describe the claimed genus.

(Ans. 10).

The Examiner argues that the "specification recites no structure required for Coleopteran-pesticide activity. The necessary and sufficient structural elements of a protein with Coleopteran-pesticidal activity are not described" (Ans. 10).

The Examiner also contends regarding the 14 disclosed variants that the "full scope of nucleic acids encompassed by the claims are not described. For example, the specification does not describe the structure of any nucleic acid encoding a Coleopteran pesticidal protein with 362 amino acid substitutions distributed over the full length of SEQ ID NO: 2" (Ans. 30).

Appellants respond that the "claimed invention is directed to nucleotide sequences having specific structural and biological properties" (App. Br. 25). Appellants contend that "[a]ll of the pending claims recite a functional limitation and also require a predictable structure of at least 90% sequence identity to SEQ ID NO: 1" (App. Br. 26). Appellants also argue that the

> specification provides fourteen (14) active variants which share between 38% and 92% identity across the full length of SEQ ID NO: 1. When local alignments are performed between the truncated active variants and nucleotides 1 to 2007 of SEQ ID NO: 1, the percent identity of the active variants to SEQ ID NO: 1 ranges between 68% to 100% sequence identity.

(App. Br. 28).

In view of these conflicting positions, we frame the written description issue before us as follows:

Does Appellants' Specification contain a written description sufficient to show they had possession of their claimed invention at the time the application was filed, as required by Federal Circuit precedent?

Findings of Fact

26. The Specification describes the complete nucleic acid sequence of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 15, 17, 19, 21, 23, 27, 28, 29, 31, 33, 39, 41, 43, and 45 as well as the complete amino acid sequence of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 16, 18, 20, 22, 24, 30, 32, 34, 40, 42, 44, and 46 (*see* Spec. 11: 18, 11:28-29).

27. The Specification discusses variants with 90% to 95% sequence identity to the desired sequences (Spec 18:29-30).

28. The Specification teaches that "[t]he inventors reasoned that the toxicity of *Cry*8-1ike proteins, and specifically the toxicity of the *Cry*8 protein, could be improved by targeting the region located between alpha helices 3 and 4 of domain 1 of the endotoxin protein" (Spec. 25:13-15).

29. The Specification teaches that "alpha helices 4 and 5 of domain 1 of *Cry*3A δ-endotoxins had been reported to insert into the lipid bilayer of cells lining the midgut of susceptible insects" (Spec 25:16-18).

30. The Specification teaches that "amino acid additions and/or substitutions are generally based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, charge, size, and the like" (Spec. 28:5-7).

31. The Specification discloses a number of mutant sequences of SEQ ID NO: 1 which retain varying levels of pesticidal activity (*see* Spec. 68, Table 1, 70, Table 2).

Discussion of 35 U.S.C. § 112, first paragraph written description rejection

We agree with the Appellants that the Specification adequately describes the genus of nucleic acids having at least 90% identity with SEQ ID NO: 1 recited in claim 1. Claim 1 is directed to a nucleic acid defined by two properties: (1) it is at least 90% identical to SEQ ID NO: 1 and (2) it encodes a protein that has pesticidal activity towards a pest in the order Coleoptera (*see* Claim 1). We note that if claims with 90% sequence identity are described, *a fortiori*, the dependent claims with narrower 93%-95% sequence identity are also described.

> "The written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ...

> i.e., complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics.'"

Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 964 (Fed. Cir. 2002).

The instant facts comply with many of the factors cited by *Enzo* as demonstrating compliance with the written description requirement. Not only is the complete primary nucleic acid sequence of SEQ ID NO: 1 disclosed along with a number of mutations (*see* FF 26-27), but the tertiary structure of two other members of the *Cry* δ-endotoxin family is known from prior art crystallization studies (*see* FF 9, 12, 15-18). These crystal structures, along with detailed mutation studies, have been used to identify specific domains within the *Cry* δ-endotoxin family (*see* FF 17). The Specification provides guidance regarding the structure of the endotoxin, noting that a "comparison of the amino acid sequences of *Cry* toxins of different specificities reveals five highly conserved sequence blocks. Structurally, the δ-endotoxins comprise three distinct domains, which are, from the N- to C-termini: a cluster of seven alpha-helices implicated in pore formation, three anti-parallel beta sheets implicated in cell binding, and a beta sandwich." (Spec. 24: 10-14).

The Specification directly couples structure with function in demonstrating that truncation mutations which remove much of the extracellular domain while retaining the alpha helices involved in pore formation have pesticidal activity, the activity associated with the pore region of the protein (*see* FF 4, 28, 29). The Specification particularly

associates the region located between alpha helices 3 and 4 of domain 1 of the endotoxin protein as being associated with toxicity (FF 29). In addition, the Specification discusses mutations at protease cleavage sites within SEQ ID NO: 1 and shows the effects of these mutations on toxicity (FF 5). Lastly, the Specification notes that conservative mutations will generally have lesser impacts on function (FF 30).

The prior art couples the structure of domains II and III to protein function, recognizing that domains II and III are involved in binding to receptors and determining specificity of the toxin for Coleoptera species (FF 12). De Maagd further identifies six blocks within Domain III and determines the effects of replacement of these blocks on insect specificity and toxicity of the protein (*see* FF 13, 14).

The facts in this case are readily distinguishable from the facts in *Lilly* or *Kubin*. In *University of California v. Eli Lilly and Co.*, 119 F.3d 1559 (Fed. Cir. 1997), the court held that claims generically reciting cDNA encoding vertebrate or mammalian insulin were not adequately described by the disclosure of cDNA encoding rat insulin. *Id.* at 1568. The court held that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus.

Id. at 1568. The *Eli Lilly* court held that a fully described genus is one for which a person skilled in the art can "visualize or recognize the identity of the members of the genus." Here, as Appellants have pointed out, the Specification and prior art provide significant guidance regarding which structural features in the *Cry*8 δ-endotoxin are responsible for pore formation, for insect specificity and for toxicity (*see* App. Br. 27-28). The Specification and prior art also describe many different amino acid changes that can be made in the wild-type sequence without affecting the toxicity of the protein (*see* FF 31).

We also think that this result is not in conflict with the precedential decision of the Board in *Kubin*, where the Board found that a claim to nucleic acids encoding a polypeptide with 80% identity to a region of a specific sequence and which polypeptide binds CD48 failed the written description requirement. *See Ex Parte Kubin*, 83 USPQ2d 1410, 1416, 1417 (BPAI 2007). In *Kubin*, the applicants disclosed nucleic acids encoding the NAIL protein at issue and fusion proteins comprising NAIL, but did not disclose any variants in the region where 80% identity was required. *Id.* at 1415. "The Specification [did] not disclose a correlation between function (binding to CD48) and structure responsible for binding to CD48 (other than the entire extracellular domain)." *Id.* at 1416.

Indeed, the *Kubin* decision shows that little was disclosed in the art or in the applicants' specification about the NAIL protein other than it was a receptor on the surface of NK cells (*id.* at 1412), that it bound to CD48 (*id.*), its amino acid sequence (*id.* at 1415), and the part of its sequence corresponding to its extracellular domain (*id.*). This is in contradistinction

to the current fact pattern in which δ-endotoxins are an extremely well characterized family of proteins, with the cited references disclosing the complete tertiary crystal structures, as well as dozens, if not hundreds, of different mutations in each of the well characterized domains of the δ-endotoxin protein (*see* FF 8-10, 12-19, 26-31). Angsuthanasombat alone teaches the effect of eight mutations targeted towards helices 4 and 5 of domain 1 of the δ-endotoxins (FF 17).

We are not persuaded by the Examiner's argument that there is insufficient written description because Appellants' fourteen "variants are very similar to one another. The full scope of nucleic acids encompassed by the claims are not described" (Ans. 30). In *Capon*, the court noted that "[i]t is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention." *Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005). In the instant case, we have found significant information to characterize the generic invention, ranging from the capacity to generate, identify and screen members of the genus, to large numbers of different mutations which characterize structure/function relationships, to information on the primary, secondary and tertiary physical structure of the δ-endotoxins (*see* FF 1-31).

Thus, the Specification does describe the recited genus sufficiently to allow a person skilled in the art to determine whether a given protein that is 90% identical to SEQ ID NO: 1 is within the scope of the instant claims. We therefore reverse the rejection of claim 1 under 35 U.S.C. § 112, first

paragraph, written description. The rejection of claims 2-3, 9-12, 17-19, 38, 43, 46, 49, 52, and 55-64 is also reversed.

CONCLUSION

In summary, we reverse the rejection of claim 1 under 35 U.S.C. § 112, first paragraph, scope of enablement and under 35 U.S.C. § 112, first paragraph, written description. The rejection of claims 2-3, 9-12, 17-19, 38, 43, 46, 49, 52, and 55-64 is also reversed.

REVERSED

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